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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *
* * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * *

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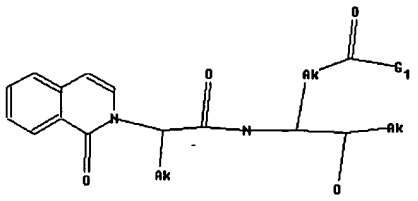

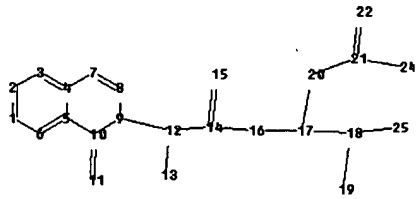

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chain nodes :
11  12  13  14  15  16  17  18  19  20  21  22  24  25
ring nodes :
1  2  3  4  5  6  7  8  9  10
chain bonds :
9-12  10-11  12-13  12-14  14-15  14-16  16-17  17-18  17-20  18-19  18-25  20-21
21-22  21-24
ring bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10
exact/norm bonds :
4-7  5-10  7-8  8-9  9-10  9-12  10-11  12-13  14-15  14-16  16-17  17-20  18-19
18-25  20-21  21-22  21-24
exact bonds :
12-14  17-18
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6
isolated ring systems :
containing 1 :


G1:O,N

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS
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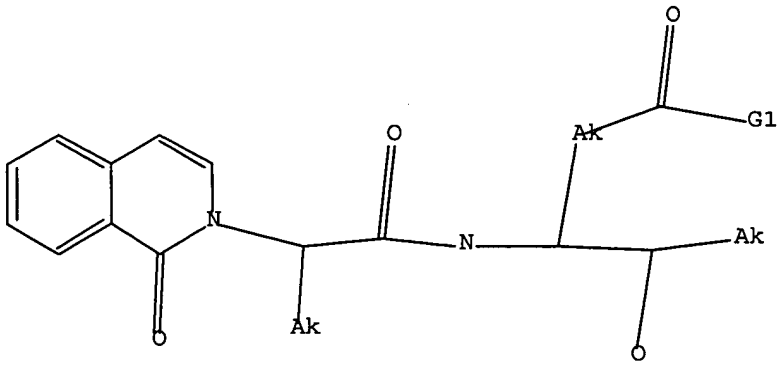

G1 O,N

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 full
L3            2 SEA SSS FUL L1

=> dis l3 1-2

L3   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   640286-58-4  REGISTRY
ED   Entered STN:  22 Jan 2004
CN   Pentonic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-
     oxobutyl]amino]-2,3,5-trideoxy-5-fluoro-, 1,1-dimethylethyl ester (9CI)
     (CA INDEX NAME)
FS   STEREOSEARCH
MF   C22 H28 Cl F N2 O5
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
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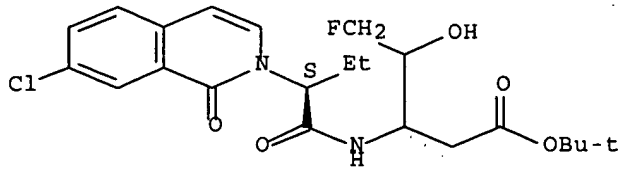
Absolute stereochemistry.

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               2 REFERENCES IN FILE CA (1907 TO DATE)
               2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3   ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   344461-29-6  REGISTRY
ED   Entered STN:  03 Jul 2001
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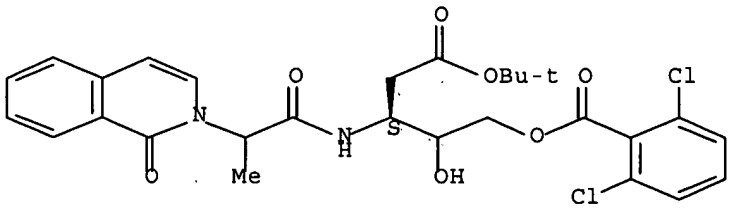
CN D-glycero-Pentonic acid, 2,3-dideoxy-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]-, 1,1-dimethylethyl ester, 5-(2,6-dichlorobenzoate), (4ξ)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H30 Cl2 N2 O7
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
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(PD<20021200)
L5 1 L4 AND PD<DEC 2002

=> dis l5 bib abs hitstr

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:435047 CAPLUS Full-text
DN 135:46192
TI Synthesis and use of heterocyclic substituted-amido halopentanoate derivatives as caspase inhibitors
IN Golec, Julian; Charifson, Paul; Charrier, Jean-Damien; Binch, Hayley
PA Vertex Pharmaceuticals Incorporated, USA
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001042216	A2	20010614	WO 2000-US33260	20001208 <--
WO 2001042216	A3	20020228		

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            YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
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            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2393710          AA    20010614    CA 2000-2393710        20001208 <--
     BR 2000016282       A     20020827    BR 2000-16282          20001208 <--
     EP 1244626          A2    20021002    EP 2000-988026         20001208 <--
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     JP 2003516393       T2    20030513    JP 2001-543517         20001208
     NZ 519424           A     20040326    NZ 2000-519424         20001208
     ZA 2002004390       A     20030602    ZA 2002-4390           20020531
     NO 2002002656       A     20020806    NO 2002-2656           20020605 <--
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OS   MARPAT 135:46192
GI
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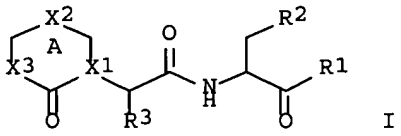

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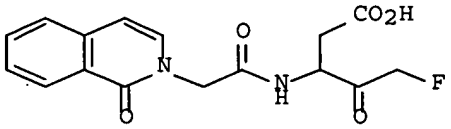

II

AB Compds. I and their synthesis are claimed [wherein; R1 = H, CN, CHN2, (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, COOH (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. For instance; substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.


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IT   344461-29-6P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (synthesis and use of heterocyclic substituted-amido halopentanoate
        derivs. as caspase inhibitors)
RN   344461-29-6  CAPLUS
CN   D-glycero-Pentonic acid, 2,3-dideoxy-3-[[1-oxo-2-(1-oxo-2(1H)-
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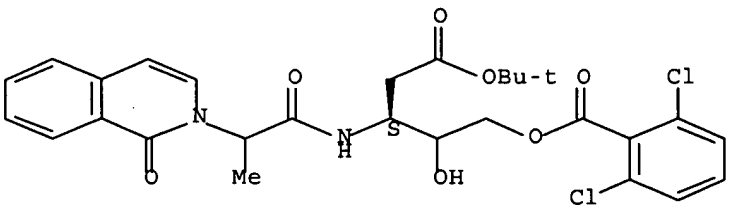
isoquinolinyl)propyl]amino]-, 1,1-dimethylethyl ester, 5-(2,6-dichlorobenzoate), (4ξ)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L3            2 S L1 FULL

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L4            4 S L3
L5            1 S L4 AND PD<DEC 2002

=> s l4 not l5
L6            3 L4 NOT L5

=> dis l6 1-3 bib abs

L6   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2004:565214  CAPLUS Full-text
DN   141:106388
TI   Preparation of 4-oxo-3-(1-oxo-1H-isoquinolin-2-ylacetylamino)-pentanoic
     acid ester and amide derivatives as caspase inhibitors
IN   Charrier, Jean-Damien; Mortimore, Michael; Studley, John R.
PA   Vertex Pharmaceuticals Incorporated, USA
SO   PCT Int. Appl., 104 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 2004058718        A1    20040715    WO 2003-US40870         20031222
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
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         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
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CA 2511235	AA	20040715	CA 2003-2511235	20031222
AU 2003303345	A1	20040722	AU 2003-303345	20031222
US 2004192612	A1	20040930	US 2003-743563	20031222
EP 1581501	A1	20051005	EP 2003-814289	20031222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1745065	A	20060308	CN 2003-80109285	20031222
JP 2006513220	T2	20060420	JP 2004-563916	20031222
PRAI US 2002-435133P	P	20021220		
WO 2003-US40870	W	20031222		

OS MARPAT 141:106388

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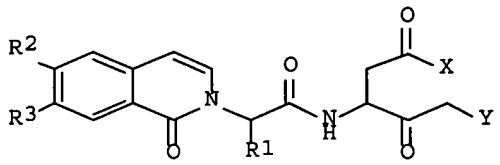

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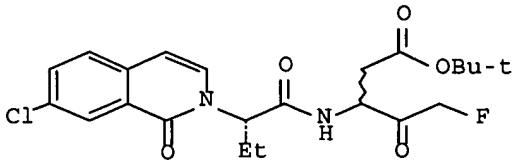

II

AB The title compds. of formula I [X = alkoxy, (substituted) NH2, etc.; Y = halo, trifluorophenoxy, tetrafluorophenoxy; R1 = alkyl; R2, R3 = H, halo, OCF3, CN, CF3] are prepared The present invention also provides pharmaceutical compns. and methods using such compns. for treating a caspase-mediated disease, particularly in the central nervous system. Thus, II was prepared from 7-chloroisochromen-1-one (preparation given), (S)-2-aminobutyric acid tert-Bu ester and 3-amino-5-fluoro-4- hydroxypentanoic acid tert-Bu ester.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:20662 CAPLUS Full-text

DN 140:77410

TI Preparation of isoquinolinone and quinazolinone peptide derivatives as caspase inhibitors

IN Knegtel, Ronald; Mortimore, Michael; Studley, John; Millan, David

PA Vertex Pharmaceuticals Incorporated, USA

SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004002961	A1	20040108	WO 2003-US20557	20030627
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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2493646	AA	20040108	CA 2003-2493646		20030627
AU 2003248758	A1	20040119	AU 2003-248758		20030627
US 2004072850	A1	20040415	US 2003-609147		20030627
BR 2003012232	A	20050510	BR 2003-12232		20030627
EP 1539701	A1	20050615	EP 2003-762231		20030627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2005533825	T2	20051110	JP 2004-518103		20030627
NO 2005000851	A	20050329	NO 2005-851		20050217
PRAI US 2002-392592P	P	20020628			
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WO 2003-US20557	W	20030627			

OS MARPAT 140:77410
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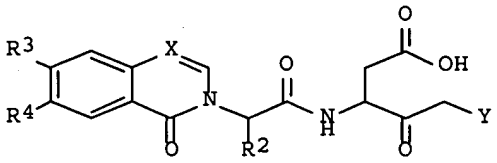

I

AB The invention relates to isoquinolinones and quinazolinones I [X is CH or N; Y is halo, tri- or tetrafluorophenoxy; R2 is alkyl; R3 is H, halo, OCF3, CN, or CF3; R4 is groups R3 or alkylthio, (un)substituted Ph, phenoxy, or phenylthio; with the proviso that when Y is halo, then R3 and R4 are not both H] which are caspase inhibitors useful in compns. for the treatment of various diseases, conditions, or disorders. Thus, I (X = CH, Y = F, R2 = Et, R3 = H, R4 = Cl), prepared by coupling of (S)-2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)butyric acid (preparation given) with 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester, had Ki (M-1 s-1) > 500,000 for inhibition of caspase-1 or caspase-3, Ki 100,000-500,000 for inhibition of caspase-8, and IC50 < 1 μM for inhibition of interleukin-1β secretion.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:991174 CAPLUS Full-text
DN 140:28050
TI Synthesis of peptide heterocyclic derivatives as caspase inhibitors
IN Golec, Julian M. C.; Charifson, Paul S.; Charrier, Jean-Damien; Binch, Hayley
PA UK
SO U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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OS MARPAT 140:28050

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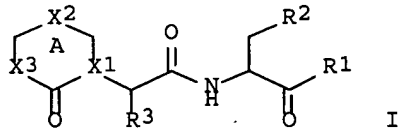

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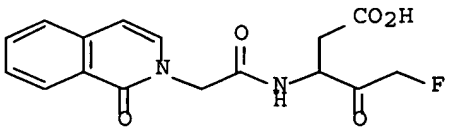

II

AB Compds. I and their synthesis are claimed [R1 = H, CN, CHN2, (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, CO2H (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. Thus, substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	16.20	187.15

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.00	-3.00

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